participants to distinguish between participants who have Gilbert's Syndrome from participants experiencing an adverse reaction to the drug that is the subject of the clinical drug trial. Additionally, participants can be eliminated or included on the basis of whether such participants possess the genetic basis of Gilbert's Syndrome. Further, the present invention is of particular interest in regards to the interpretation of the results obtained from the clinical drug trial.

B. Brief Summary of the Office Action and Response

In the Office Action, claims 1-13 were rejected under 35 U.S.C. 112(1). Additionally, the claims were also objected to for allegedly containing the following informalities: claims 10-14 were objected to for being misnumbered and claim 13 recites specific sequences, however no corresponding SEQ ID NOS were provided.

In the present Amendment, claims 1-13 have been amended. Thus, claims 1-13 are pending. The amendments to the existing claims are fully supported in the specification and, thus, no new matter is added.

C. Remarks

With respect to the objection to the claims being misnumbered, the claims have been amended as required.

With respect to the Examiner' objection to claim 13 for failure to provide SEQ ID NOS, claim 13 has been amended to incorporate the SEQ ID NOS, which were previously submitted on May 4, 2000, as required.

Rejections Under 35 U.S.C. § 112(1)

Claims 1-13 stand rejected under 35 U.S.C. 112, first paragraph. The Office Action alleged that the subject matter was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The Applicant respectfully traverses the rejection of claims 1-13 for the reasons set forth below.

The Applicant strongly asserts that the present invention does enable one skilled in the art to make and/or use the invention. The Applicant respectfully submits that the present invention is directed to a method for increasing the efficacy of clinical drug trials and is not drawn to a method for screening for a drug.

During the Clinical Phase, drug trials involve administering a potential candidate agent or drug, which was previously identified in the drug screening stage to human participants in order to ascertain whether that agent causes any side effects and helps alleviate symptoms of the disease under study.

At the outset, the Applicant acknowledges that the Examiner correctly noted that 'the results of experiments involving screening for a drug or the efficacy of a drug trial is not predictable." However, this is ***not*** the aim of the present invention. The present invention is ***not*** involved in drug screening, but is in fact, involved in carrying out clinical drug trials. Therefore, any potential candidate agents or drugs will have already been screened for in

preclinical trials and will now be undergoing ***clinical trials*** involving patients. In fact, the present invention screens ***individuals***, not potential agents, for the presence of Gilbert's Syndrome.

Further, in view of the teachings embodied in the specification, the Applicant strongly submits that one of ordinary skill in the art would undoubtedly recognize the value of the present invention and would know how to make and use the present invention to increase the efficacy of clinical drug trials. As amended, claim 1 clearly teaches a method to increase the efficacy of clinical drug trials by testing participants or potential participants exhibiting hyperbilirubineamia for the presence of Gilbert's Syndrome. As correctly noted in the specification, when high levels of serum total bilirubin are detected in a clinical drug trial participant, it is unclear whether the increase in bilirubin is subsequent to an adverse effect associated with the drug being studied or due to that individual having Gilbert's Syndrome. (Specification page 3, lines 8-15.) If a participant actually has Gilbert's Syndrome and this is not taken into account, it will appear that the drug being studied has unwanted adverse side effects. Thus, the present invention provides a method for detecting and identifying such participants, and then either removing them from the trial or taking any results from such participants, having Gilbert's Syndrome, into account when interpreting data for the drug being studied. Thus, the method does not intend to improve screening of drugs or their efficacy in participants, but instead, improves the efficacy of the ***clinical drug trials*** by identifying those participants who may influence the results of the trial as a result of their condition.

In view of this assertion, the Applicant notes that MPEP 2164.04 states "in order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." The court in *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971) held that whenever a rejection on this basis is made, that it is "incumbent upon the Patent Office . . . to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is consistent with the contested statement." (Emphasis added.) Moreover, the Examiner must present evidence that one skilled in the art would not know how to use the present invention to increase the efficacy of clinical drug trials.

Additionally, in regards to the assertion set forth in the Office Action that the "level or skill in molecular biology is high," the Applicant respectfully submits that the present invention only employs basic, standard molecular biology techniques (PCR amplification and DNA sequencing) to identify any polymorphism. Further, the Applicant submits that the present invention does not utilize any techniques unknown to the standard molecular biologist and would certainly not be beyond the skill of those persons in the relevant field.

With respect to the Examiner's objection that the claims are "broadly drawn," the Applicant submits that the Applicant is the first to identify the effect of Gilbert's Syndrome on the efficacy of clinical drug trials. Accordingly, the Applicants should be entitled to broad protection.

Finally, the Applicant respectfully contends that the present invention is not anticipated by Bosma et al. (N. Eng. J. Med., Vol. 333, No. 18, November 1995). The present invention is not the identification of a mutation associated with Gilbert's Syndrome but provides a method for the use of the known mutation to improve the efficacy of clinical drug trials. Further, Bosma et al does not teach that the mutation or syndrome can affect the results of a clinical drug trial.

For all of the reasons set forth above, the Applicant respectfully submits that claims 1-13 are in full compliance with the written description requirement of 35 U.S.C. § 112, first paragraph, and respectfully request withdrawal of the rejection.

Summary

In view of the foregoing amendments and remarks, the Applicant submit that this application is in condition for allowance and respectfully request early and favorable notification to that effect. If it would expedite prosecution of this application, the Examiner is invited to confer with the Applicant's undersigned attorney.

Respectfully submitted,

Allan Ratner, Reg. No. 19,717
Attorney for Applicant

AR/lk
Dated: June 18, 2001
Enc - Version with markings to show changes made

Suite 301
One Westlakes, Berwyn
P.O. Box 980
Valley Forge, PA 19482-0980
(610) 407-0700

The Assistant Commissioner for Patents is hereby authorized to charge payment to Deposit Account No. **18-0350** of any fees associated with this communication.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on:

June 18, 2001
Linda M. Keller

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) Use of a test in clinical drug trials as a method to improve the efficacy of such trials, [for detecting the genetic basis of Gilbert's Syndrome in a method to improve the efficacy of clinical drug trials, the method comprising] which comprises the steps of screening samples from participants or potential participants for the basis of Gilbert's Syndrome and eliminating participants having the genetic basis of Gilbert's Syndrome from the trial or including [potential] such participants in [a] the [drug] trial [in] and interpreting the results thereof based on the knowledge of [them] such participants' possessing or not possessing the genetic basis of Gilbert's Syndrome.

2. (Amended) Use of [a] the test as claimed in claim 1 wherein the method comprise the steps of:

a) taking a sample from each participant or potential participant in a clinical drug trial,

b) screening the samples for the genetic basis of Gilbert's Syndrome,

c) identifying such participants having the genetic basis of Gilbert's Syndrome, and

d) proceeding with the clinical drug[s] trial[s] based on [in] the knowledge of such participants possessing or not possessing the genetic basis of Gilbert's Syndrome.

3. (Twice Amended) Use of [a] the test as claimed in claim 1 wherein the sample is chosen from blood, buccal smear or any other sample containing DNA from the participants or potential participants.

4. (Twice Amended) Use of [a] the test as claimed in claim 1 [further comprising] wherein the method further comprises the step of eliminating participants having the genetic basis of Gilbert's Syndrome from [a] the clinical drug[s] trial.

5. (Twice Amended) Use of [a] the test as claimed in claim 1 wherein the method further comprises the [further] step of selecting only participants having the genetic basis for Gilbert's Syndrome for [a] the clinical drug[s] trial.

6. (Twice Amended) Use of [a] the test as claimed in claim 1 further comprising the step of interpreting the results of the clinical drug[s] trial [in] based on the knowledge that certain participants have the genetic basis of Gilbert's Syndrome as distinguished from participants adversely affected by the drug.

7. (Twice Amended) Use of [a] the test as claimed in claim 1 wherein the method comprises the steps of:

a) isolating DNA from each sample,

b) amplifying the DNA inner region indicating the genetic basis for Gilbert's Syndrome,

c) isolating amplified DNA fragments, and

d) identifying [individuals] participants having the genetic basis of Gilbert's Syndrome.

8. (Twice Amended) Use of [a] the test as claimed in claim [1] 7 wherein the DNA is amplified using the polymerase chain reaction (PCR) using a radioactively labeled pair of nucleotide primers.

[10] 9. (Twice Amended) Use of [a] the test as claimed in claim 7 wherein the DNA region indicating the genetic basis of Gilbert's Syndrome is the gene encoding UDP-glucuronosyltransferase (UGT).

[11] 10. (Twice Amended) Use of [a] the test as claimed in claim 7 wherein the DNA to be amplified is in an upstream promoter region of the UGT 1*1 exon 1.

[12] 11. (Twice Amended) Use of [a] the test as claimed in claims 7 wherein the DNA to be amplified includes the regions between -35 and -55 nucleotides at the 5' end of UGT 1*1 exon.

[13] 12. (Twice Amended) A kit for screening [individuals participation] participants or potential participants in clinical drug trials, wherein

the kit [comprising] comprises primers for amplifying DNA in the region of the genome indicating the genetic basis of Gilbert's Syndrome.

[14] 13. (Twice Amended) Primers for use of [a] the test as claimed in claim 1 including primer pairs, AB or CD as follows:

A/B: ([1] A,5' - AAGTGAACTCCCTGCTACCTT-3' (SEQ ID NO:1),

B,5' -CCACTGGATCAACAGTATCT-3' (SEQ ID NO:2) or

C/D: (C,5' -GTCACGTGACACAGTCAAAC-3' (SEQ ID NO:3);

D 5' -TTTGCTCCTGCCAGAGGTT-3' (SEQ ID NO:4)).